Signal Specificity in Practice and Theory

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EPA International Science Forum on Computational Toxicology

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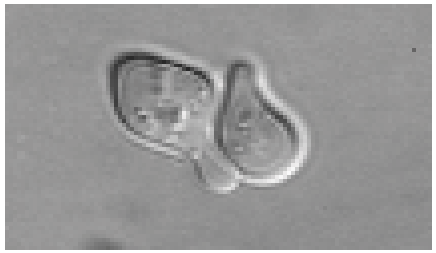
Outline

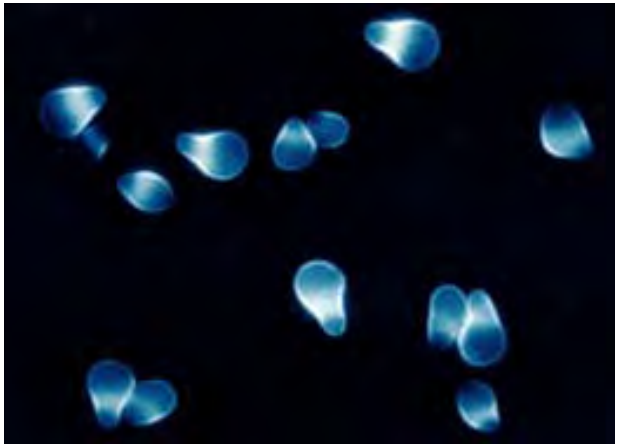
I. **Signal specificity in the yeast mating and starvation pathways**

II. Kinetic insulation as mechanism for signal specificity

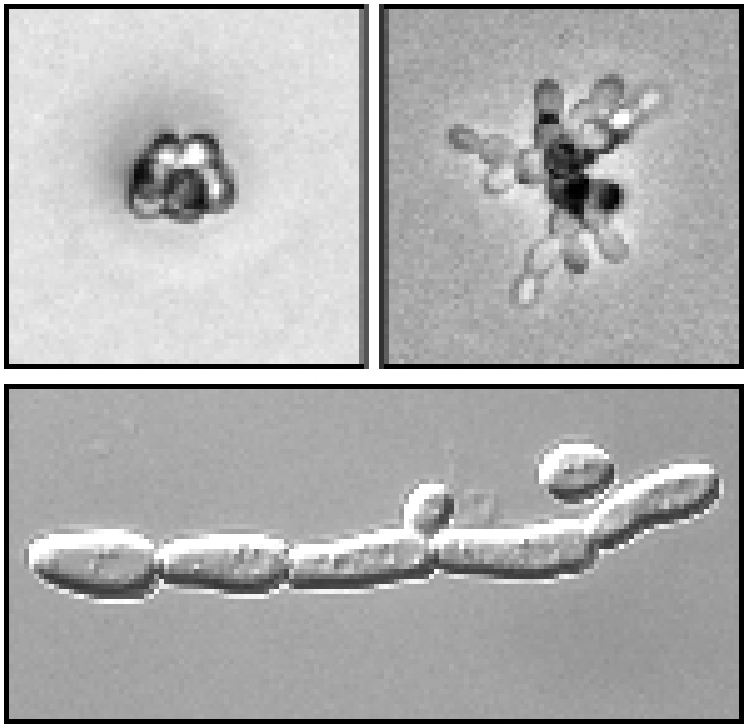
Two developmental behaviors

Mating differentiation



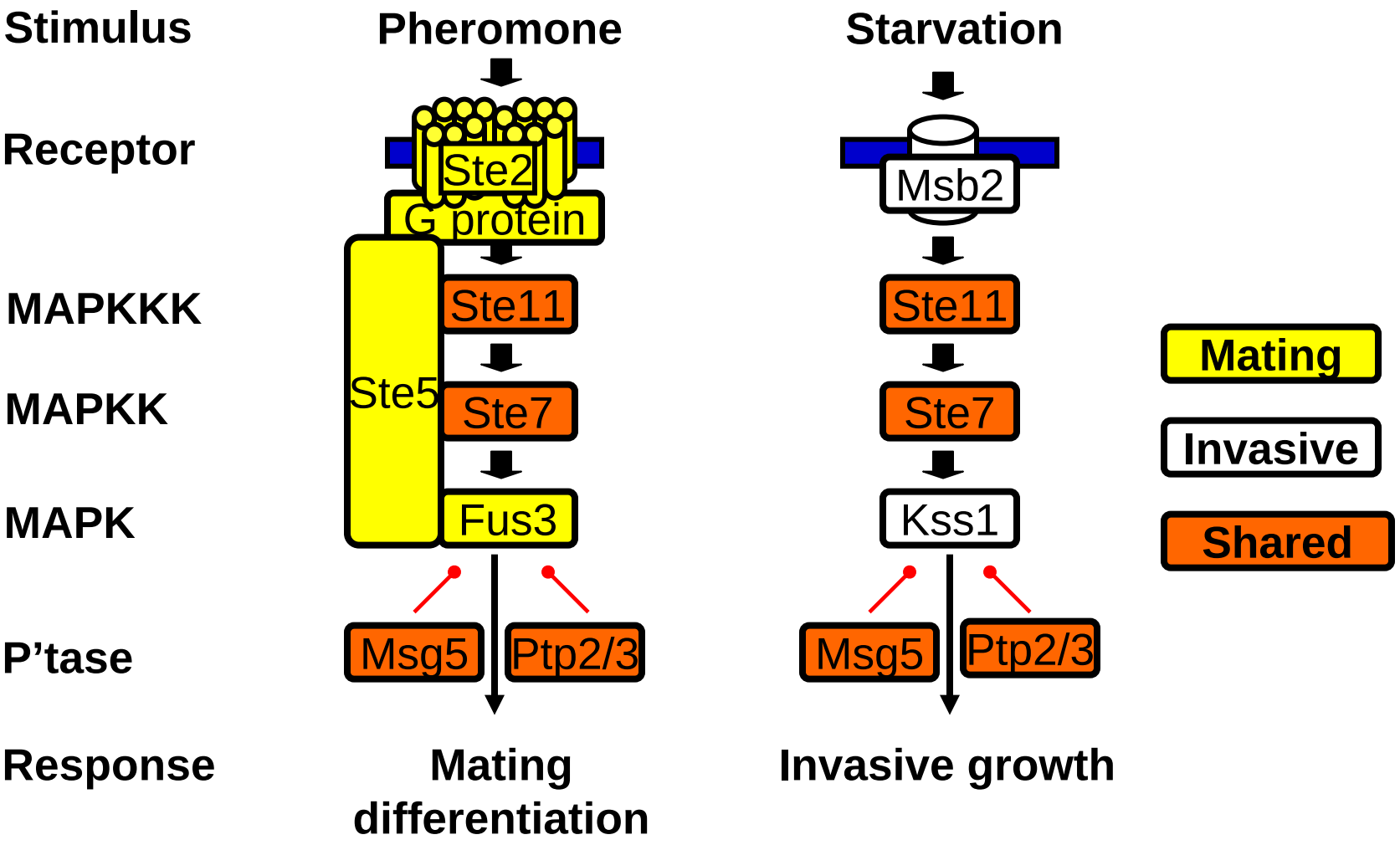


Invasive growth

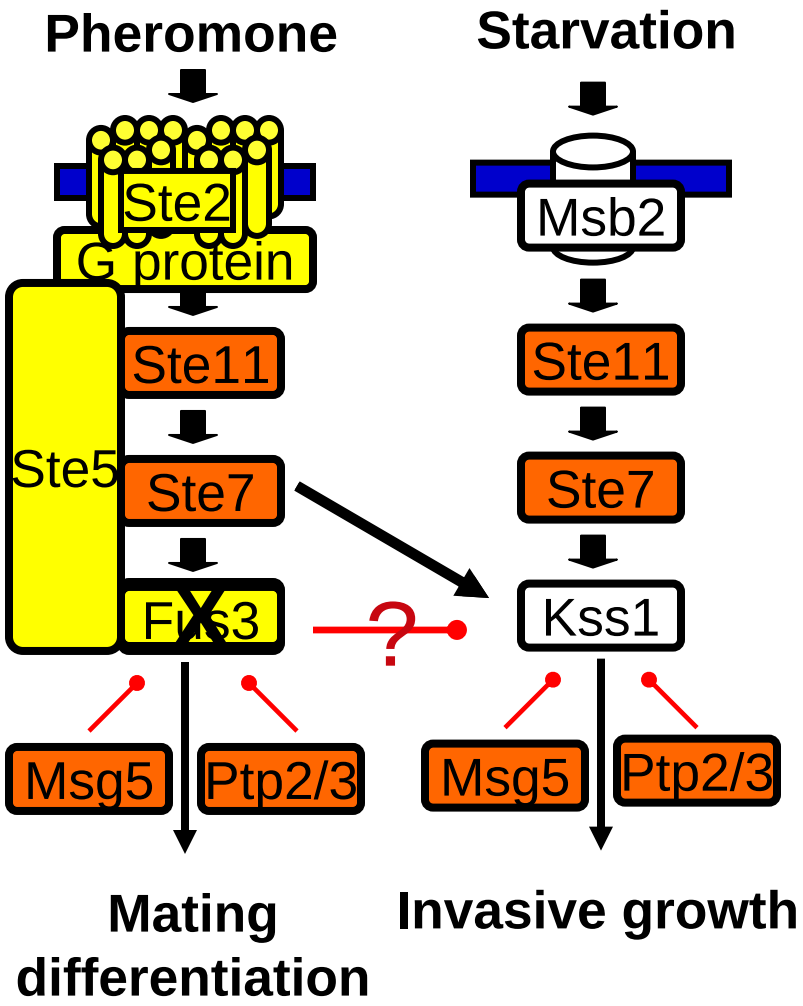


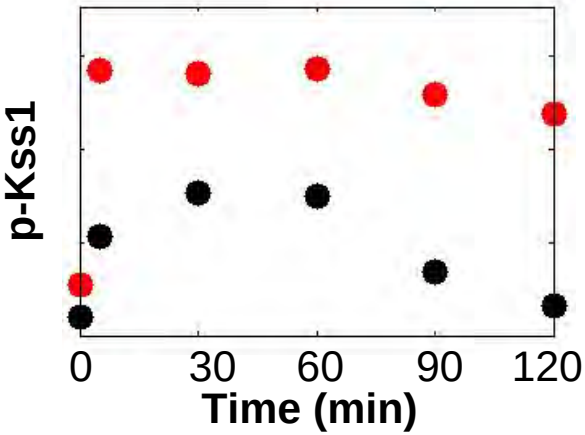
http://www.biology.buffalo.edu/faculty/cullen.html

Signaling pathways with shared components



Fus3 diminishes activation of Kss1

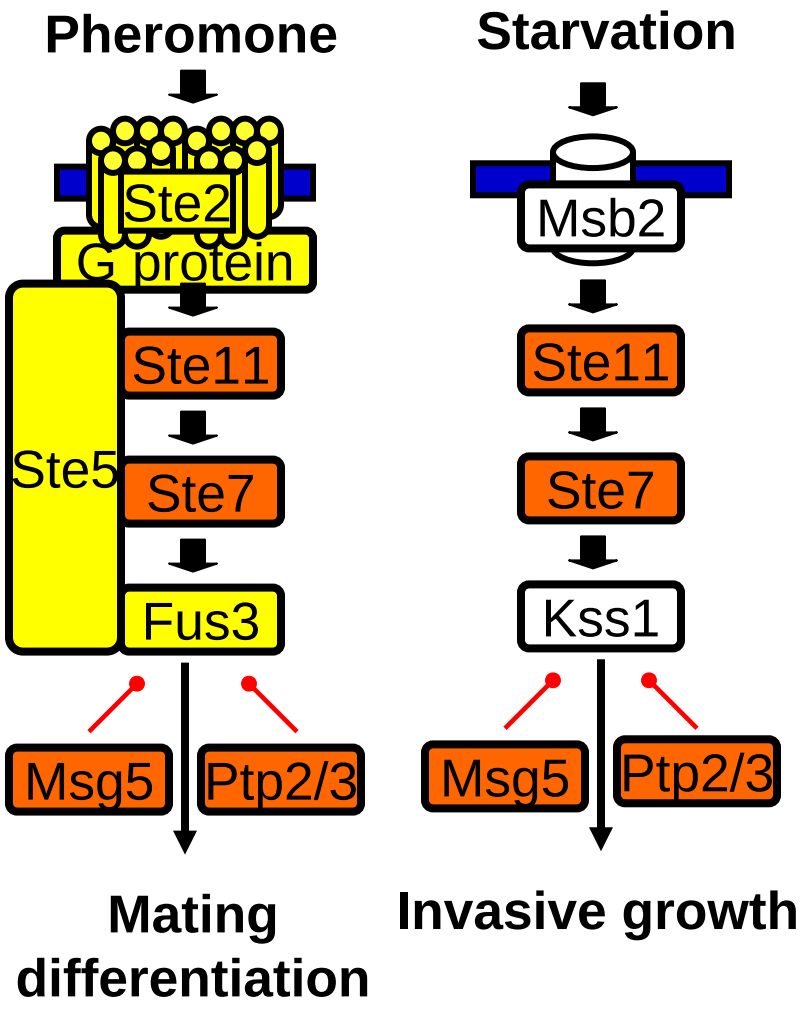


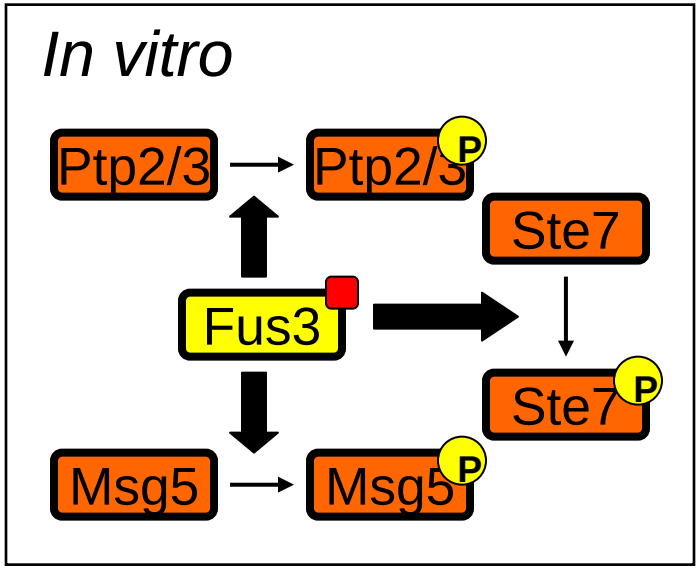


How does Fus3 diminish Kss1 activity?

W. Sabbagh, Jr., L. J. Flatauer, A. J. Bardwell, L. Bardwell, *Mol Cell* **8**, 683 (2001)

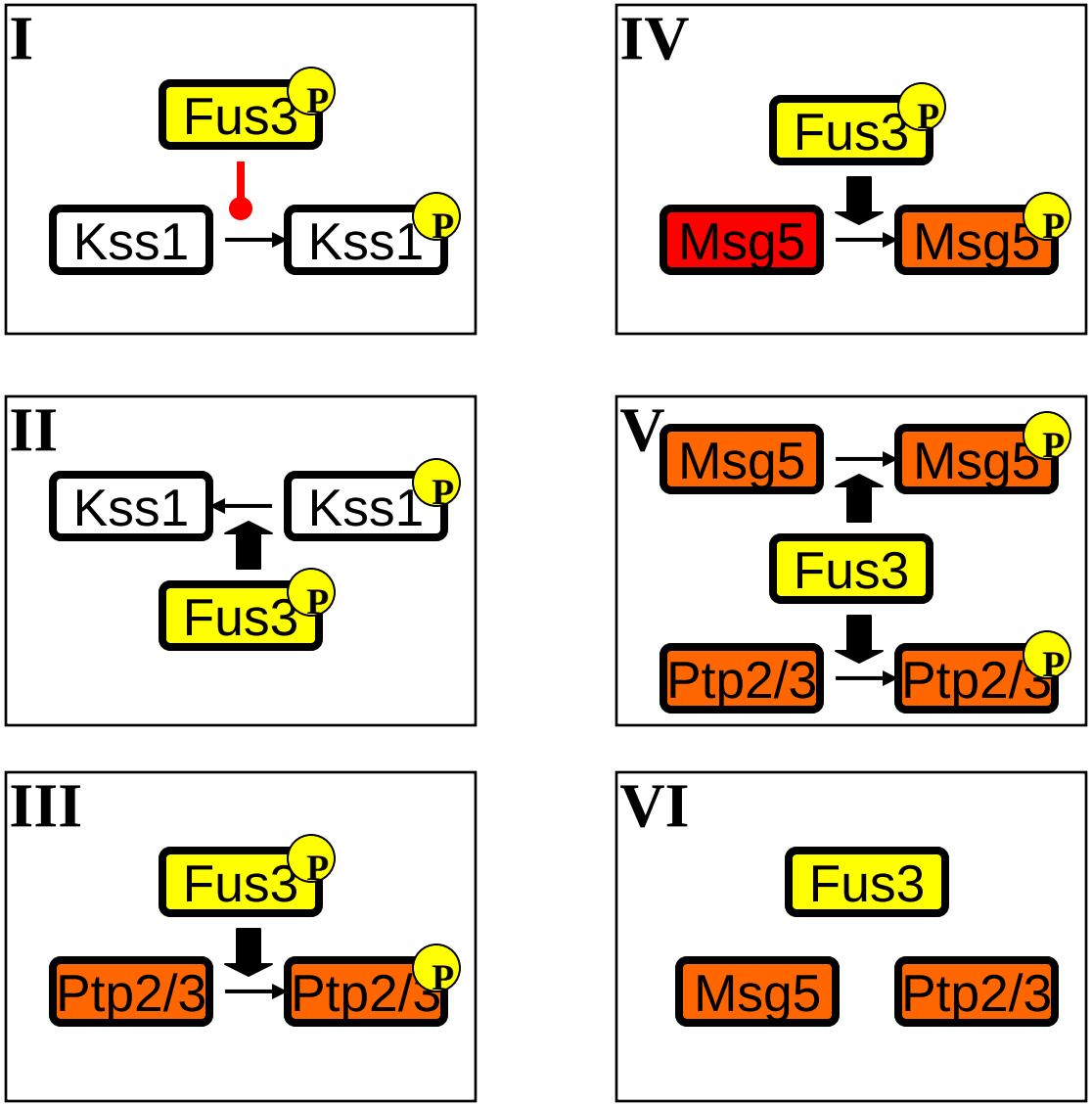
Fus3 phosphorylates shared components





Fus3 may diminish Kss1 activity by phosphorylating shared pathway components.

Six Models of Signal Specificity



Research Design

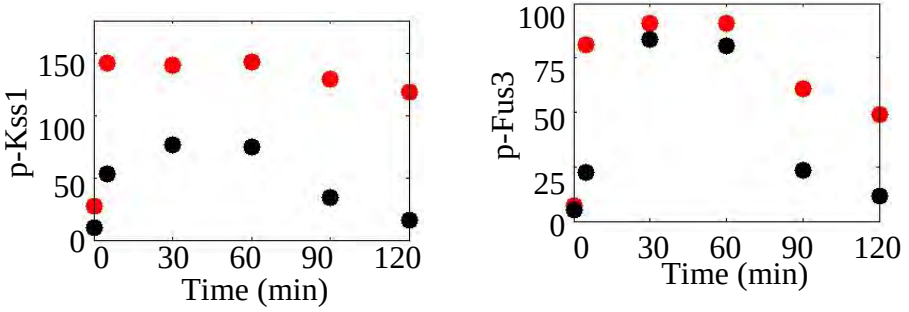
Model construction

$$\frac{d\mathbf{c}}{dt} = \mathbf{f}(\mathbf{c}, t)$$

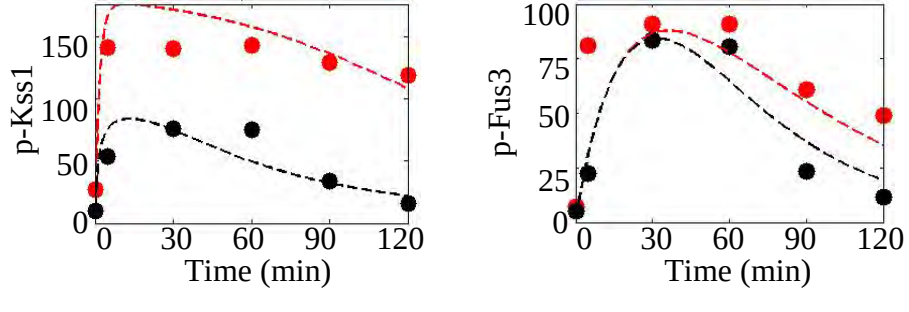
Time course of MAPK activation

IB:phospho-p42/44

Quantification by densitometry

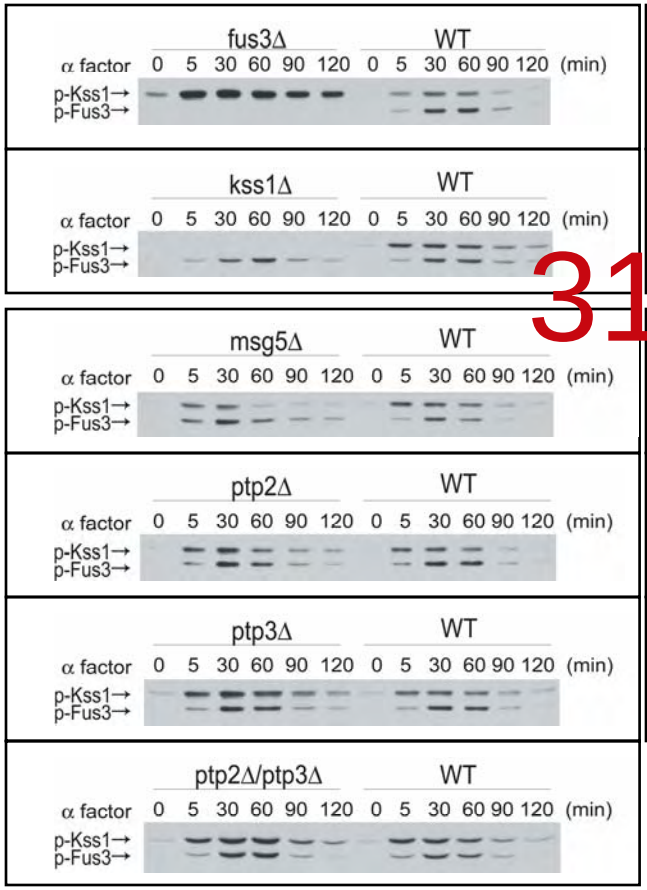


Fit models to the experimental results

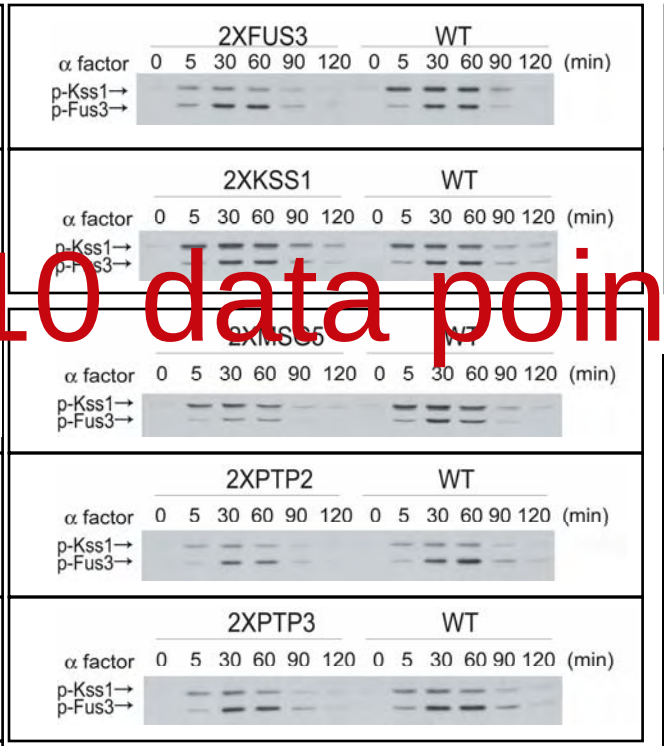


Experimental Results

Deletion

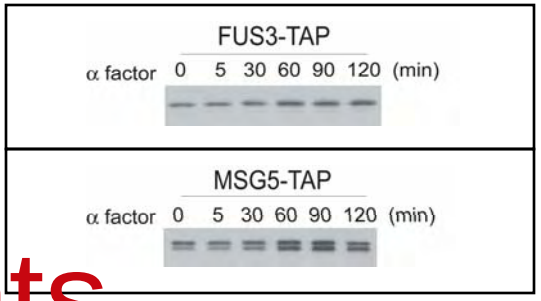


2-fold overexpression



IB:phospho-p42/44

Protein induction



310 data points

IB:protein A

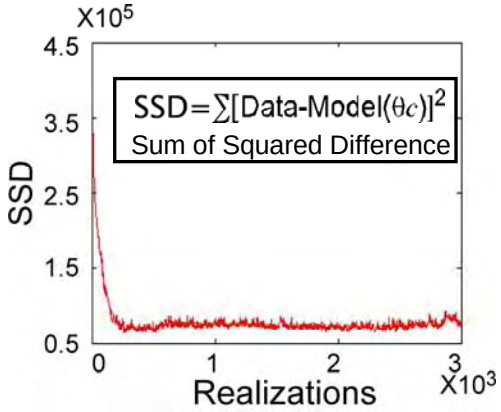
	Deletion	2-fold over expression
MAPK	fus3Δ	2XFUS3
	kss1Δ	2XKSS1
P′tase	msg5Δ	2XMSG5
	ptp2Δ	2XPTP2
	ptp3Δ	2XPTP3
	ptp2/3Δ	

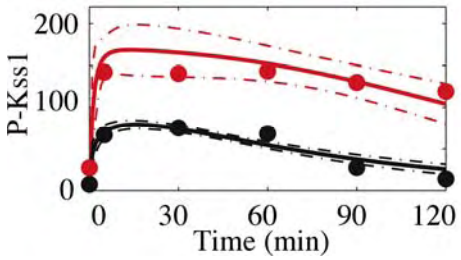
	Mutant
MAPK	$fus3^{K42R}$

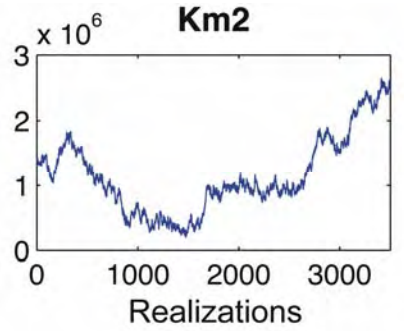
Markov Chain Monte Carlo Methods (MCMC)

Advantages

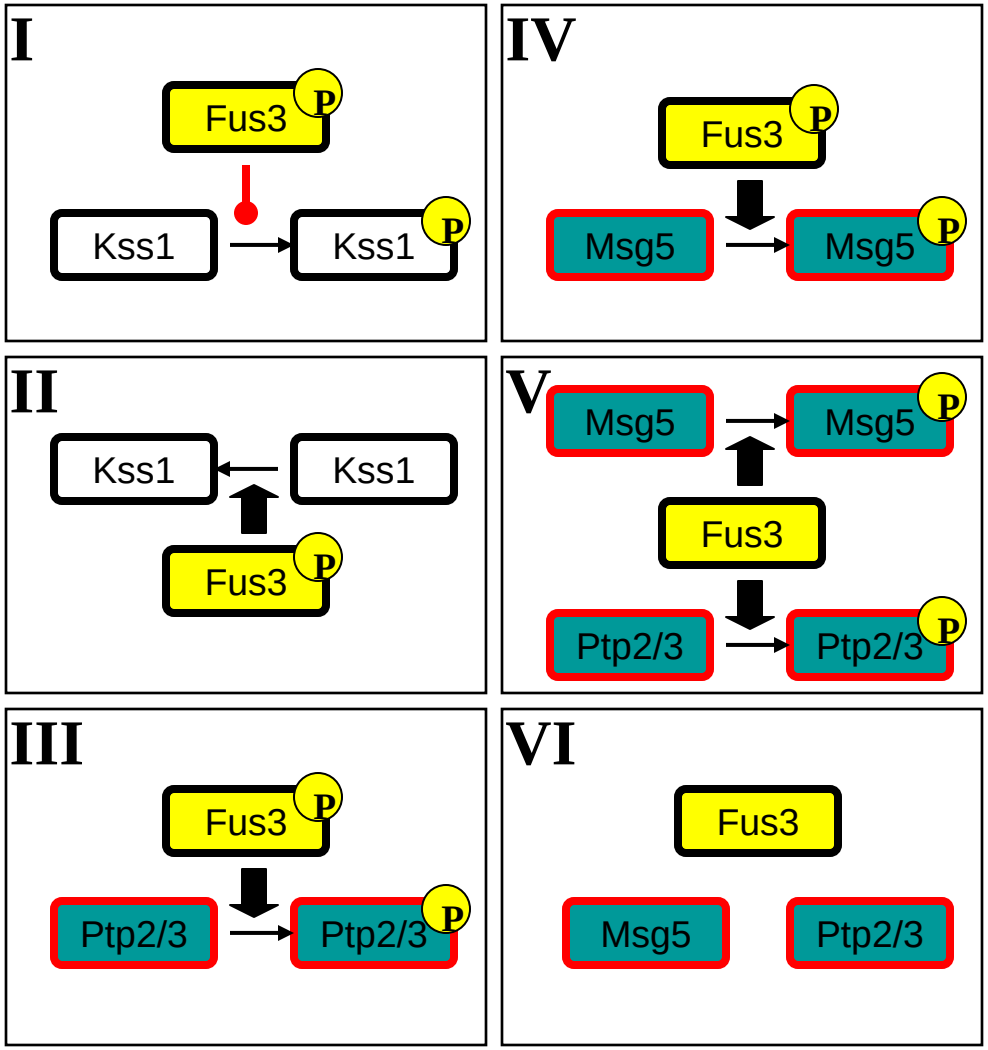
- Method generates a family of parameter sets that each produces approximately equivalent fits to the data
- Method allows confidence intervals to be placed on model outputs
- Method generates a distribution of model parameters that provides a measure of how well the experimental data constrain the model.

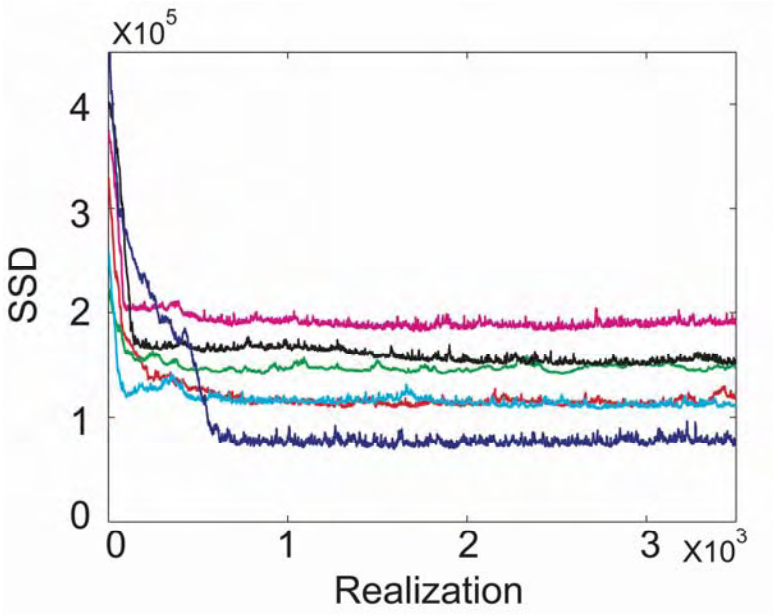


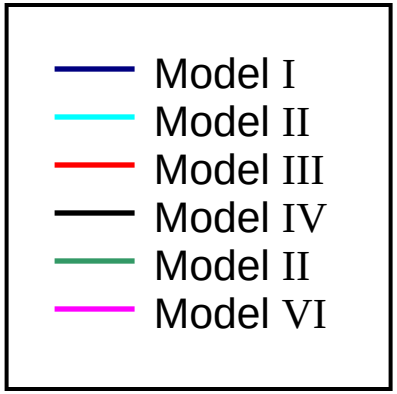




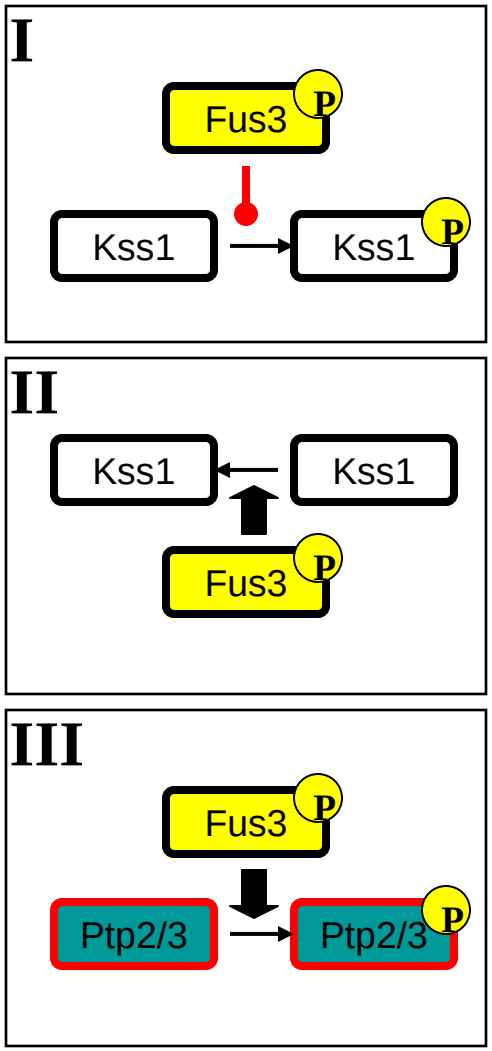
Evaluation of the Models

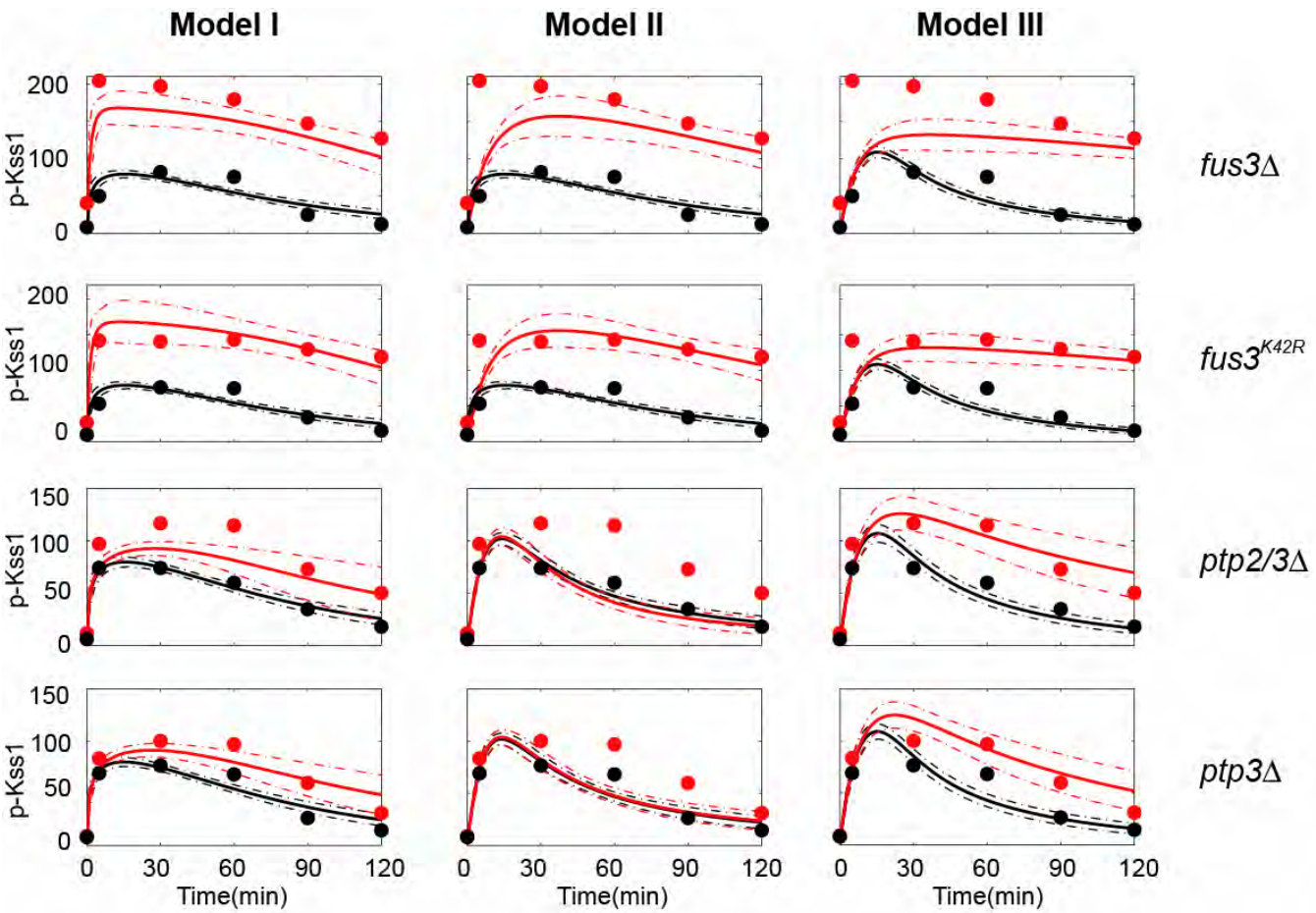




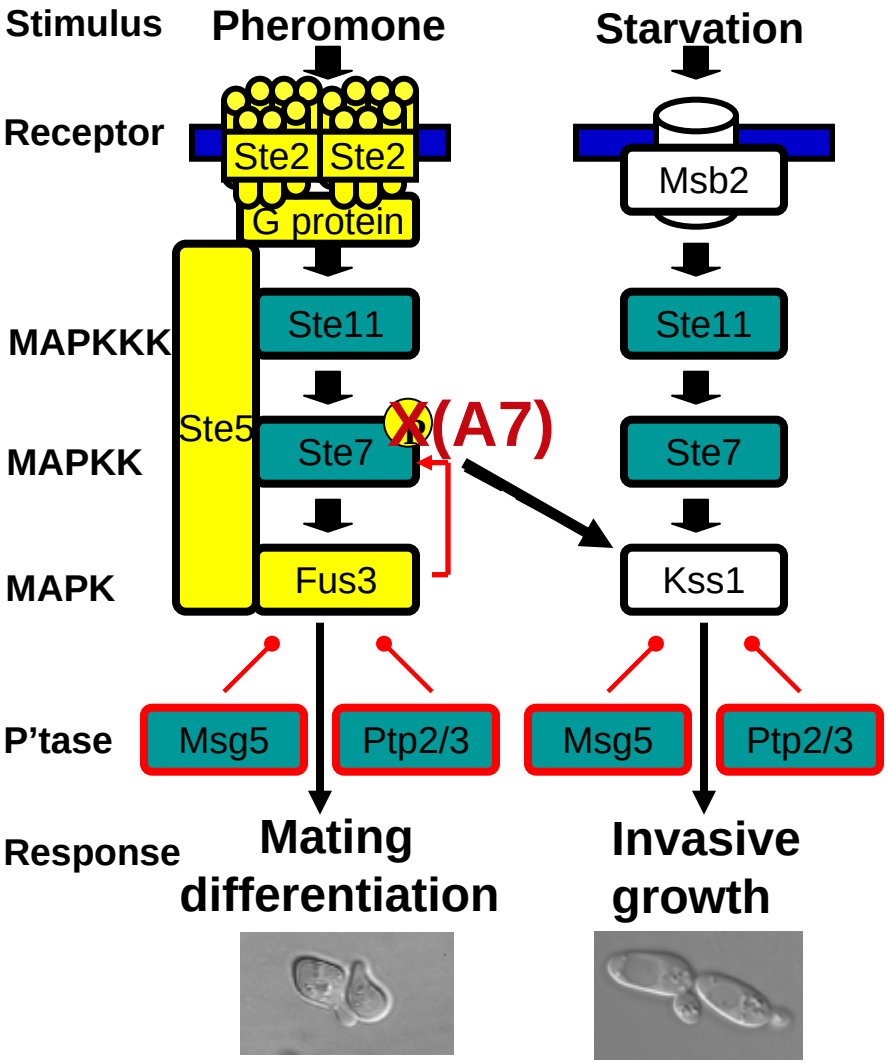


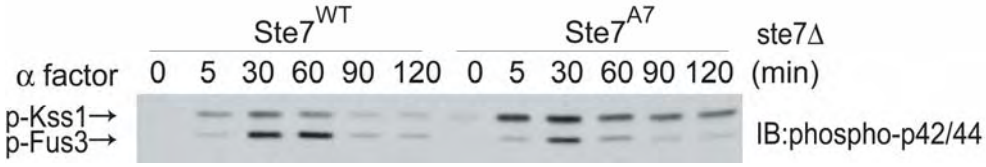
Comparison of the Models

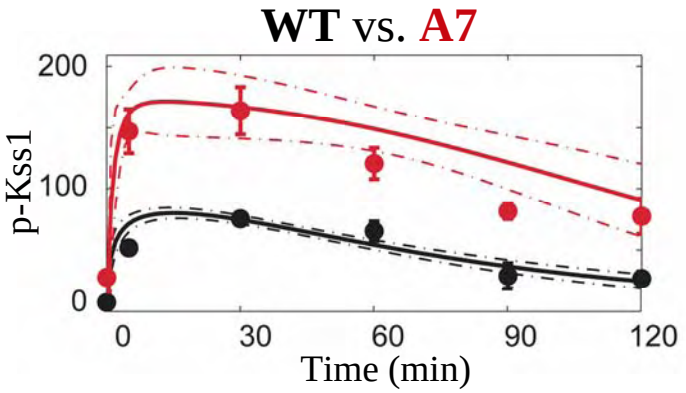




Validation of the Model I







Conclusions

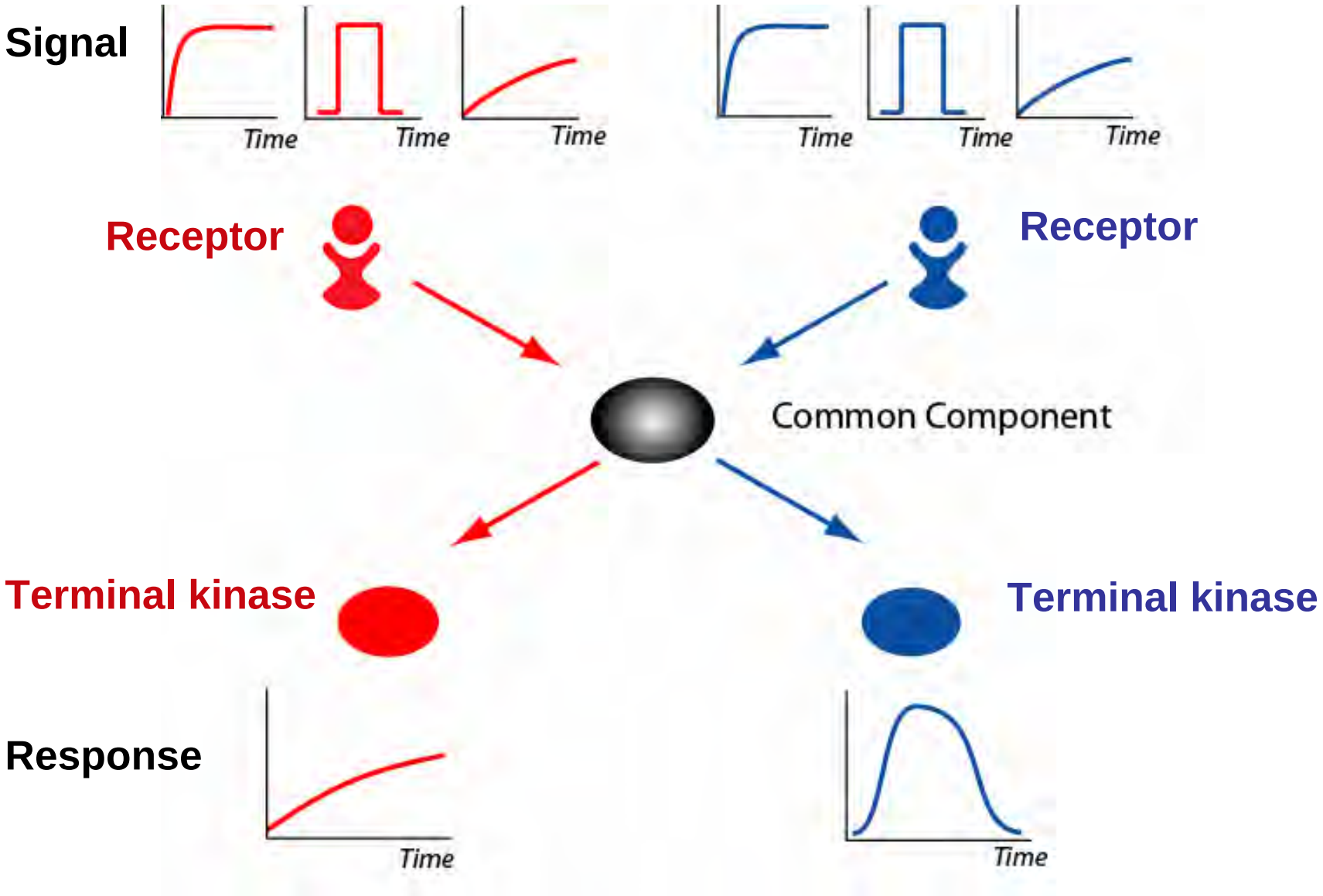
- A new mechanism of pathway specificity.
- Demonstrates utility of computational modeling in biology.

Outline

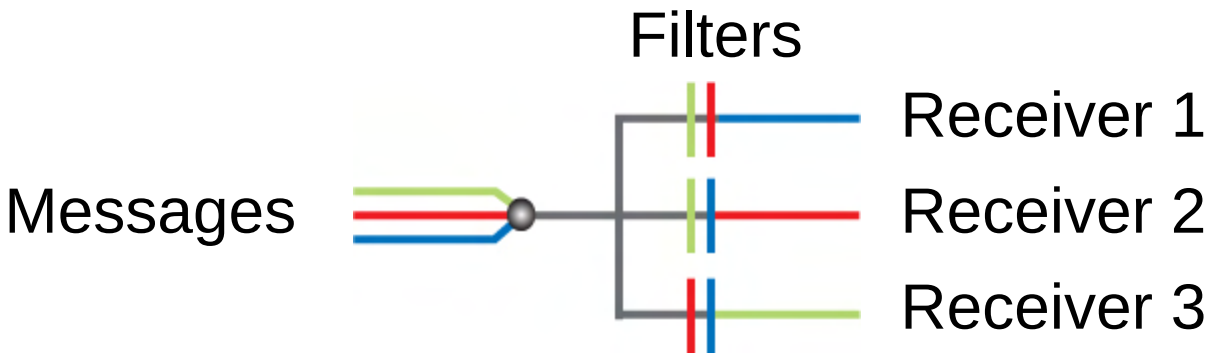
I. Pathway specificity in the yeast mating and starvation pathways

II. Kinetic insulation as mechanism for signal specificity

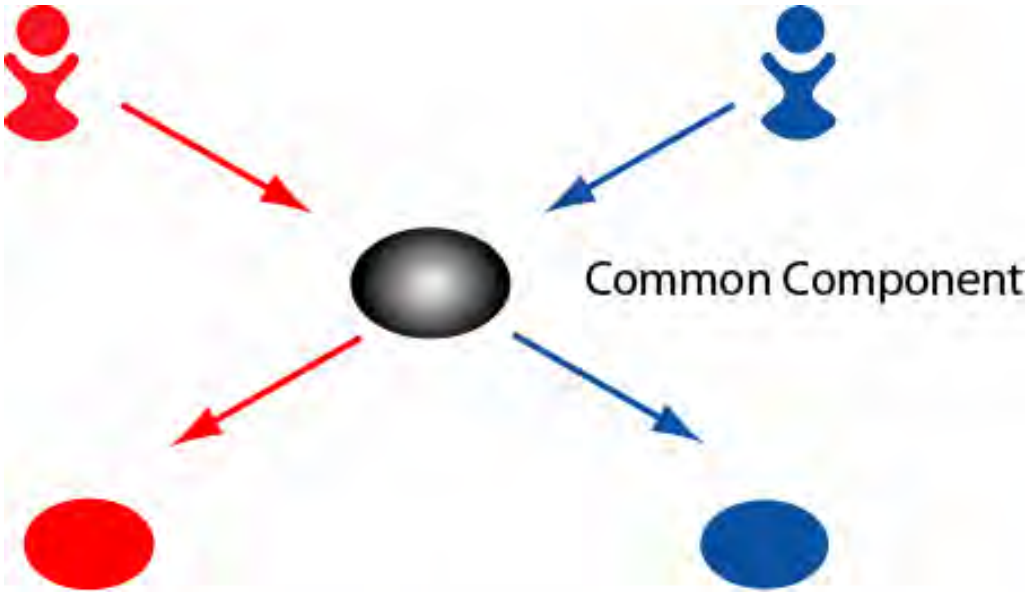
Signal Specificity



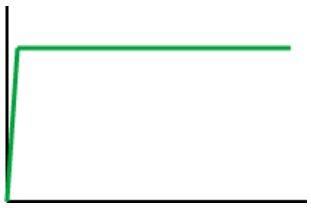
Information Transmission

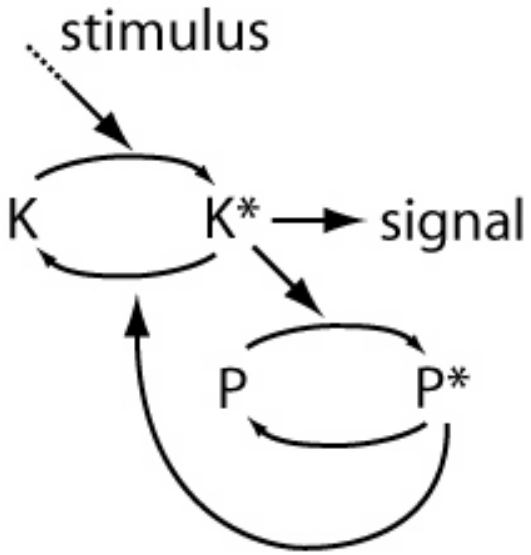


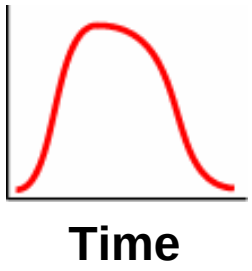
Can this approach be used in intracellular signaling networks?

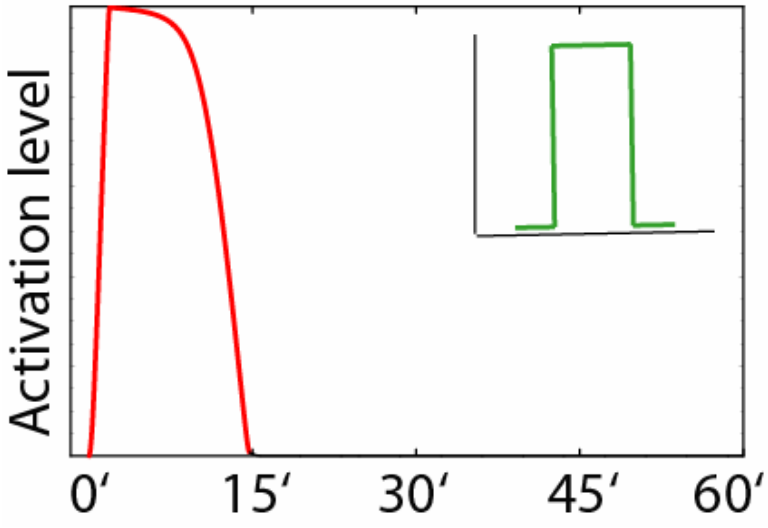


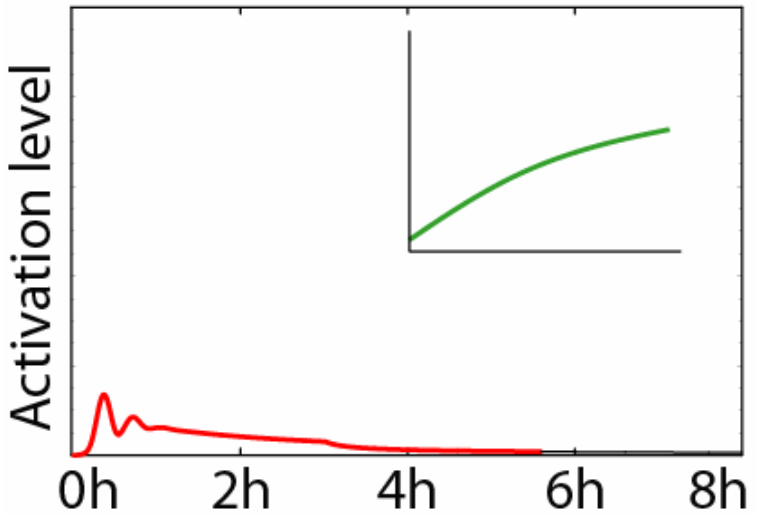
Adaptable systems act as a high pass filter





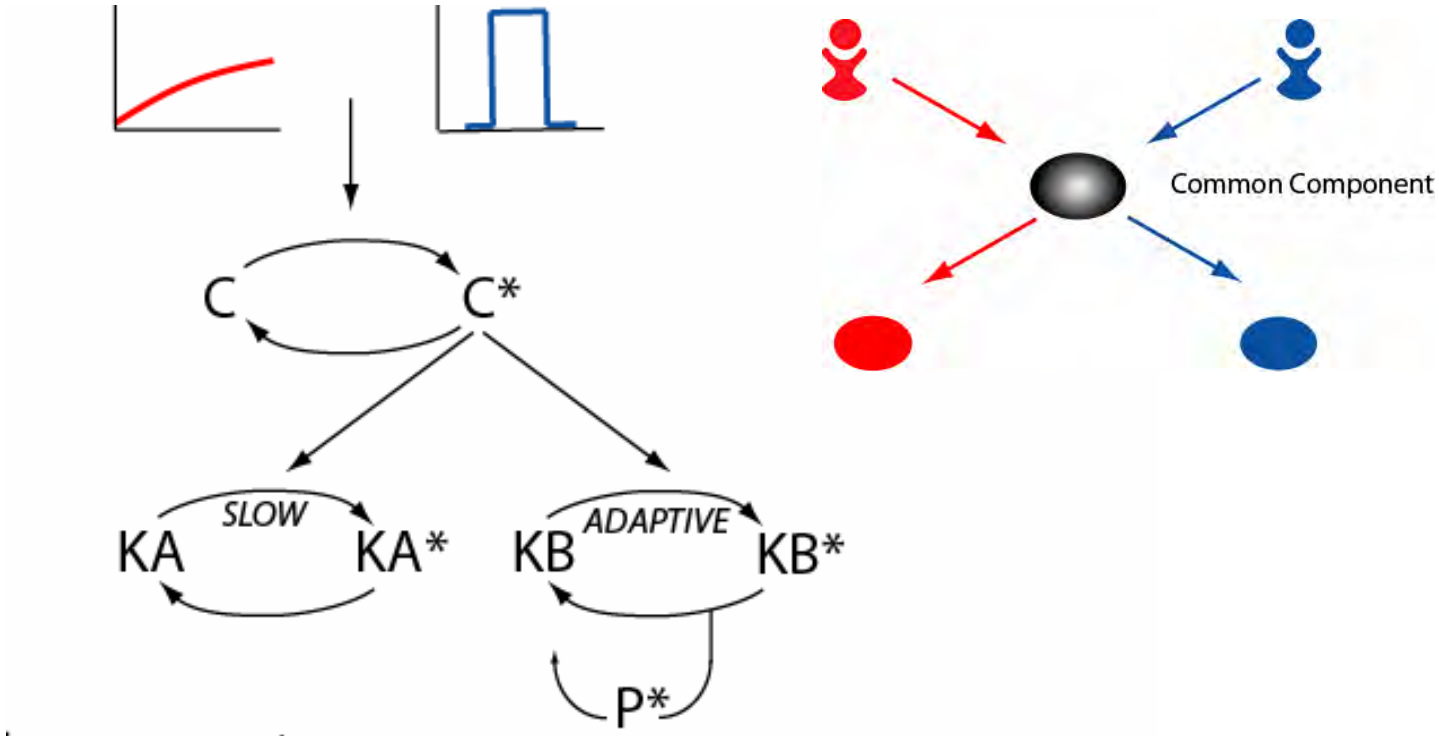






Downstream signal decoding

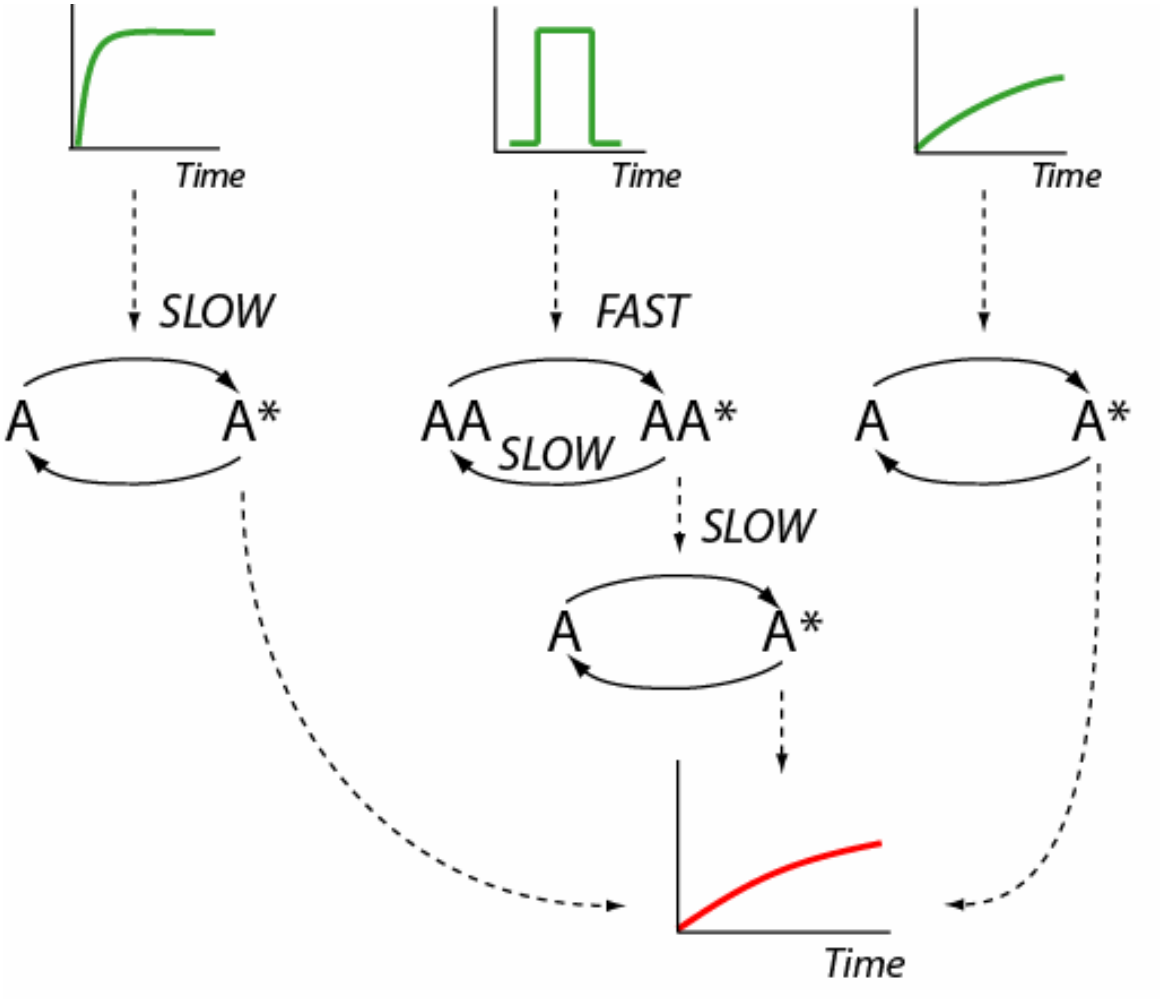
Input



Response

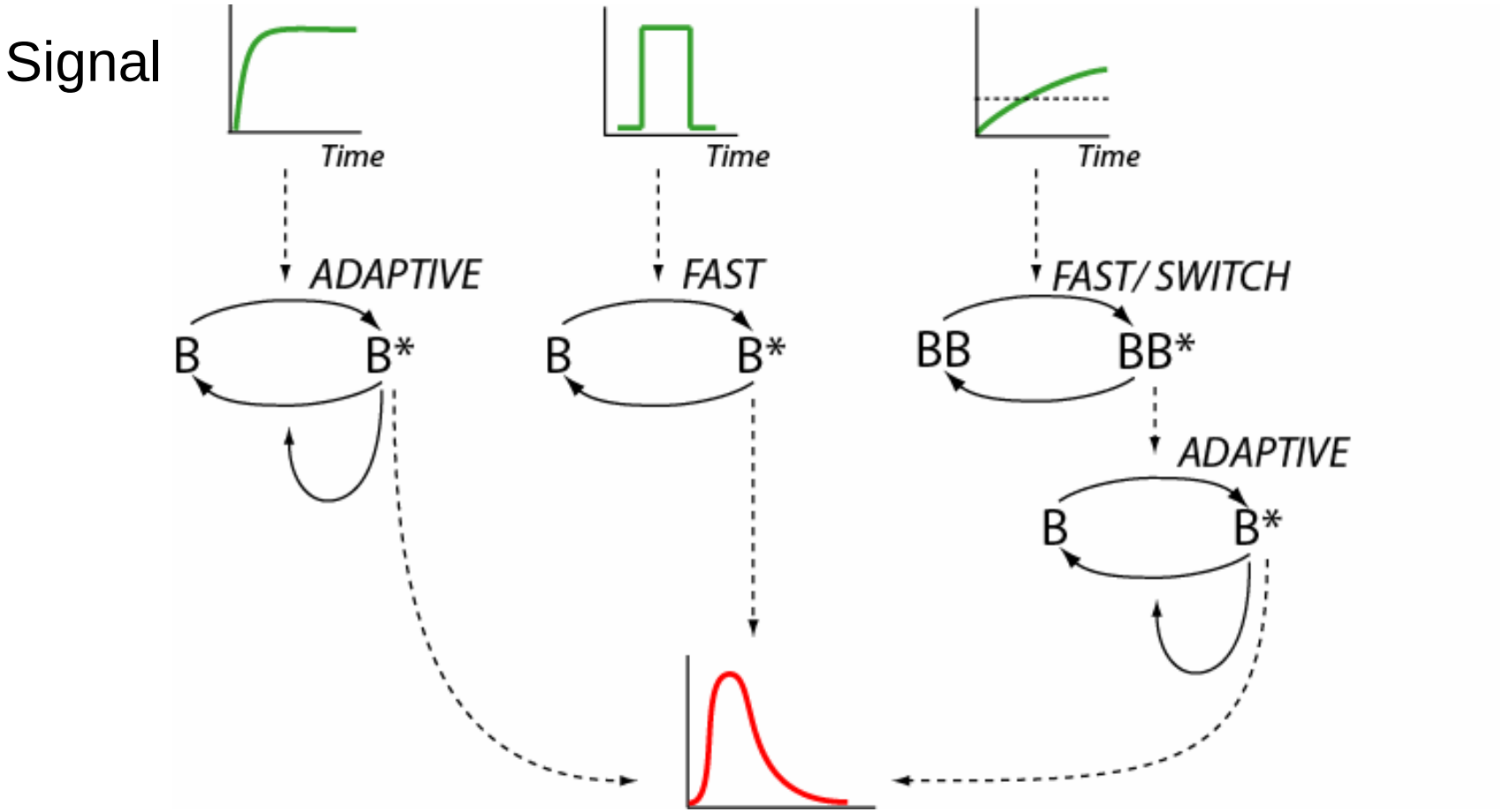
Upstream signal processing – slow response

Signal

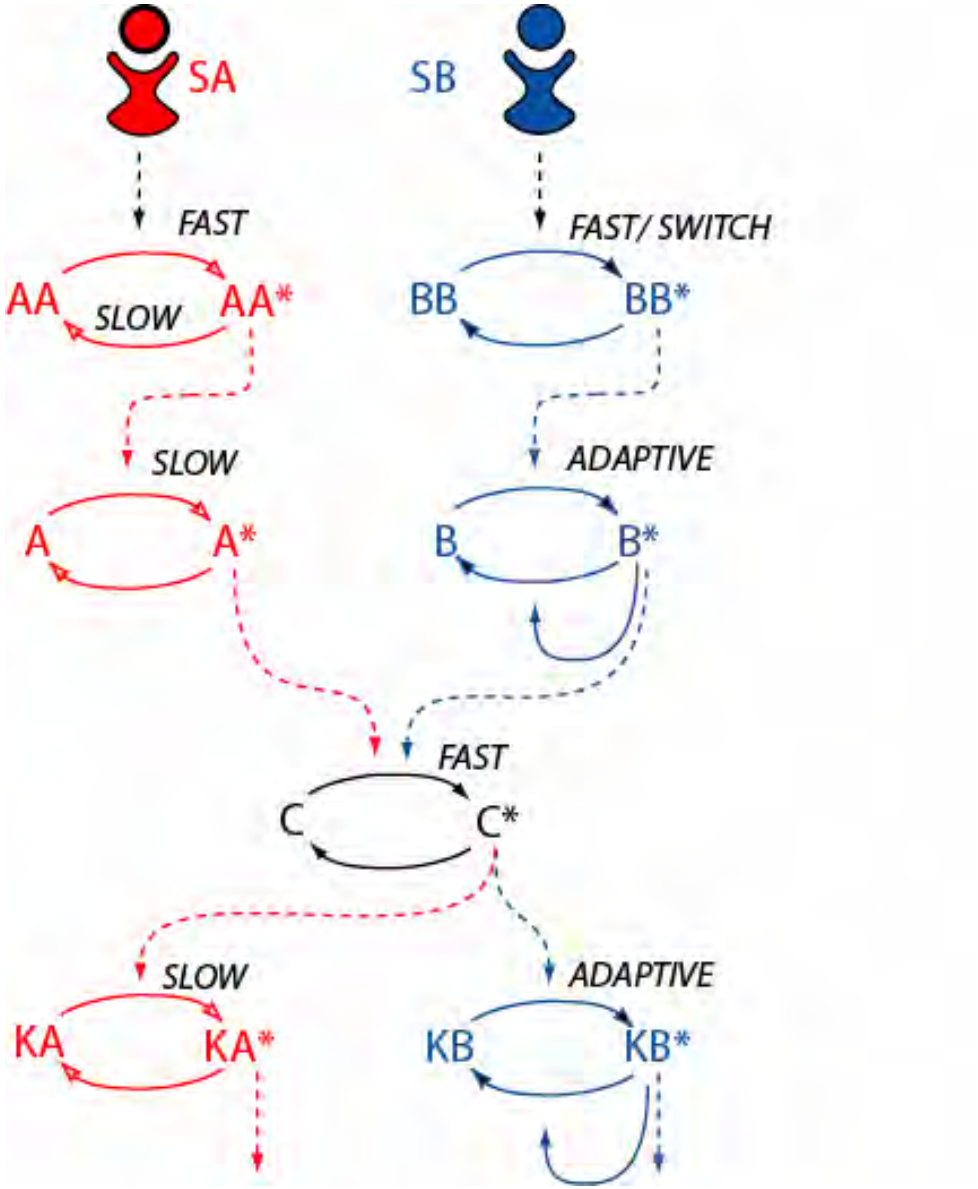


Response

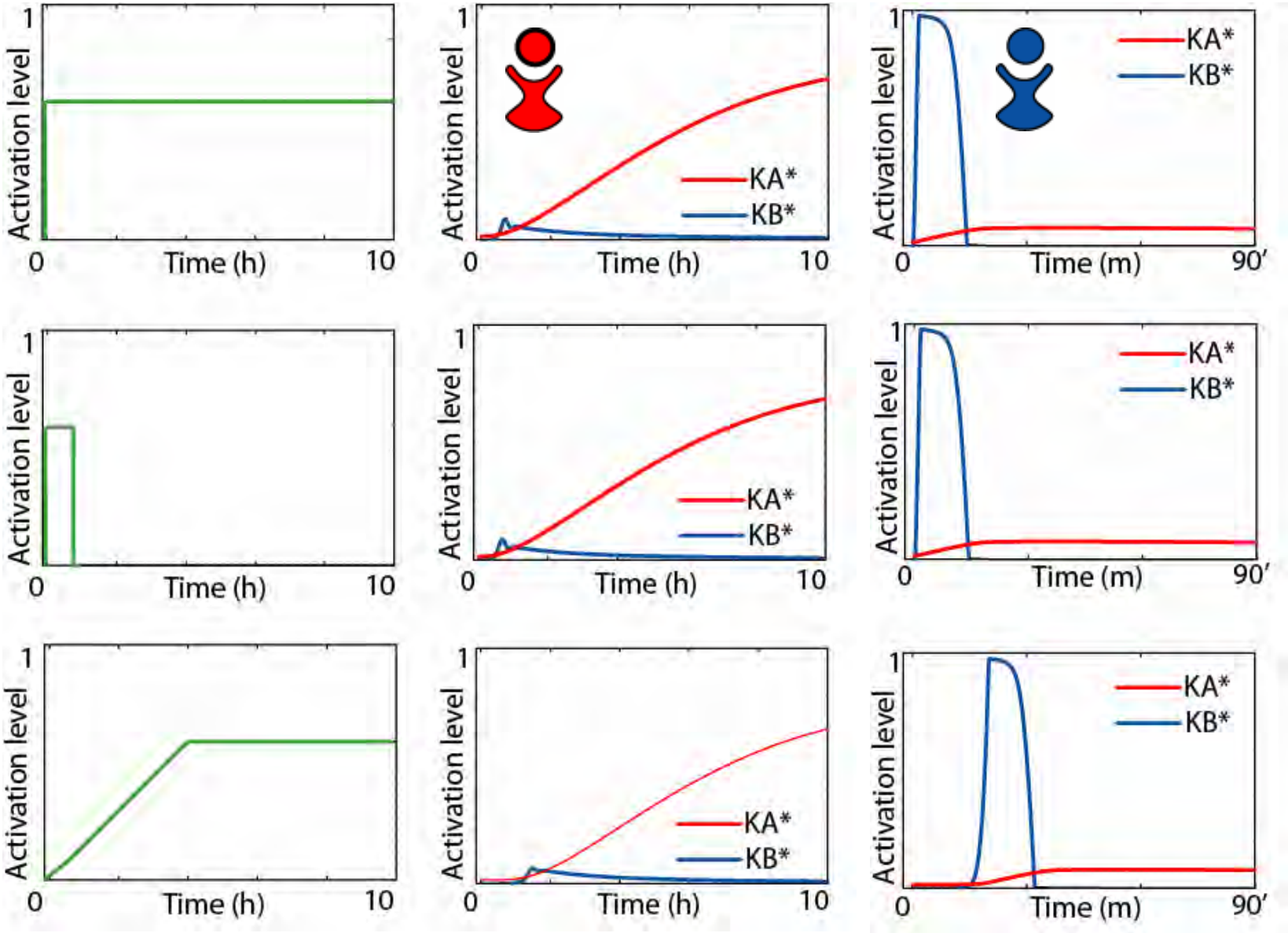
Transient response



Specificity by kinetic insulation



Simulation results



Conclusions

- Kinetic insulation provides a potential mechanism of pathway specificity.
- Specificity is based solely on the temporal profile of the transmitted signal.
- Multilevel signaling cascades may have evolved to modulate the temporal profile of pathway activity.

Acknowledgements

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